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FILE 'USPATFULL, CAPLUS' ENTERED AT 16:12:58 ON 25 MAR 2003

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L1          1 FILE USPATFULL
L2          1 FILE CAPLUS
TOTAL FOR ALL FILES
L3          2 S US6444679/PN
           SELECT L1 1 RN
L4          1 FILE USPATFULL
L5          1 FILE CAPLUS
TOTAL FOR ALL FILES
L6          2 S E8-E85
L7          290 FILE USPATFULL
L8          3826 FILE CAPLUS
TOTAL FOR ALL FILES
L9          4116 S (DELTA OPIOID) OR (DELTA-OPIOID) OR (.DELTA.OPIOID)
L10         1758 FILE USPATFULL
L11         13075 FILE CAPLUS
TOTAL FOR ALL FILES
L12         14833 S (SUBSTANCE OR CHEMICAL OR DRUG) (3A) (DEPENDENC?)
L13         31 FILE USPATFULL
L14         129 FILE CAPLUS
TOTAL FOR ALL FILES
L15         160 S L12 AND L9
L16         7 FILE USPATFULL
L17         1 FILE CAPLUS
TOTAL FOR ALL FILES
L18         8 S L15 AND SEROTONIN AND COMBIN?
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ENTER NAME OR (END):L0901362/1

L# LIST L1-L18 HAS BEEN SAVED AS 'L0901362/L'

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L41 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2003 ACS
 AN 1988:449158 CAPLUS
 DN 109:49158
 TI Analgesic and tolerance-inducing effects of the highly selective .delta.
 opioid agonist [cyclic] [D-Pen2,D-Pen5]enkephalin in mice
 AU Kovacs, Gabor L.; Nyolczas, Noemi; Krivan, Marta; Gulya, Karoly
 CS Cent. Lab., Univ. Med. Sch., Szeged, H-6720, Hung.
 SO European Journal of Pharmacology (1988), 150(3), 347-53
 CODEN: EJPHAZ; ISSN: 0014-2999
 DT Journal
 LA English
 CC 2-10 (Mammalian Hormones)
 Section cross-reference(s): 1
 AB The novel and highly selective, conformationally restricted cyclic
 enkephalin analog for .delta.-opioid receptors,
 [D-Pen2,D-Pen5]enkephalin (DPDPE; Pen = penicillamine), was studied in
 various in vivo tests for analgesia, tolerance, and phys. dependence.
 Intracerebroventricular (i.c.v.) administration of DPDPE caused a
 dose-dependent, **naloxone**-reversible antinociception, measured
 with the heat-irradiant (tail-flick) method. Acute tolerance developed to
 the antinociceptive effect of DPDPE. DPDPE also caused mild signs of
 phys. dependence (withdrawal hypothermia and body wt. loss) after repeated
 peptide treatment. Severe signs of morphine withdrawal (e.g. withdrawal
 jumping) on the other hand, could not be reversed by the administration of
 DPDPE. The activation of central .delta.-opioid receptors may play a role
 in controlling pain mechanisms, and this activation is followed by the
 rapid development of a tolerance to this action.
 ST enkephalin penicillamine analog analgesia delta receptor
 IT Analgesia
 (from enkephalin penicillamine analog, brain .delta.-receptors in)
 IT **Drug dependence**
 (on enkephalin penicillamine analog)
 IT Drug tolerance
 (to analgesia from enkephalin penicillamine analog, brain
 .delta.-receptors in)
 IT Brain, composition
 (.delta.-receptors of, analgesia from enkephalin-penicillamine analog
 mediation by)
 IT Receptors
 RL: BIOL (Biological study)
 (.delta.-, analgesia from enkephalin penicillamine analog mediation by)
 IT 88373-73-3
 RL: BIOL (Biological study)
 (analgesia from and tolerance to, brain .delta.-receptors in)
 IT 57-27-2, Morphine, biological studies
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); BIOL (Biological study)
 (tolerance to, enkephalin-penicillamine analog effect on, brain
 .delta.-receptors in)

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AN 1986:102741 CAPLUS

DN 104:102741

TI Mu- and delta-opioid receptor-mediated epileptoid responses in morphine-dependent and non-dependent rats

AU Dua, Ashok K.; Pinsky, Carl; LaBella, Frank S.

CS Fac. Med., Univ. Manitoba, Winnipeg, MB, R3E 0W3, Can.

SO Electroencephalography and Clinical Neurophysiology (1985), 61(6), 569-72
CODEN: ECNEAZ; ISSN: 0013-4694

DT Journal

LA English

CC 2-5 (Mammalian Hormones)

AB In 3 different models of opioid epileptogenesis opioid receptor antagonists were used to differentiate the nature and role of opioid receptor subtypes involved in opioid agonist-induced epileptoid responses in rats. Selective .mu.-opioid receptor agonism (morphine [57-27-2]) can initiate epileptoid responses in nondependent rats. .delta.-Opioid agonism (DADLE [63631-40-3]) is important in sustaining .mu.-initiated epileptoid responses. A role for .mu.-opioid receptor stimulation in .delta.-opioid-initiated epileptoid responses remains yet to be clarified. .delta.-Opioid antagonism (ICI 154129 [83420-94-4]) does not ppt. classic autonomic and behavioral signs of withdrawal in morphine-dependent rats but blocks epileptoid responses in naloxone-pptd. morphine withdrawal without affecting autonomic and behavioral components of an ongoing withdrawal reaction. These results with morphine-dependent rats have the interesting implication that .delta.-opioid antagonists should be useful in preventing EEG seizure activity during morphine withdrawal, esp. in treatment of life-threatening seizures often seen in newborns from addicted mothers.

ST opioid epilepsy delta mu receptor; morphine dependence seizure opioid antagonist

IT Epilepsy

(from opioids, .delta.- and .mu.-receptors mediation of)

IT **Drug dependence**

(on morphine, withdrawal from, seizures in, .delta.- and .mu.-receptors mediation of)

IT Receptors

RL: BIOL (Biological study)

(.delta.-, epilepsy from opioids mediation by)

IT Receptors

RL: BIOL (Biological study)

(.mu.-, epilepsy from opioids mediation by)

IT 57-27-2, biological studies

RL: BIOL (Biological study)

(dependence on, withdrawal from, seizure in, .delta.- and .mu.-receptors in mediation of)

IT 83420-94-4

RL: BIOL (Biological study)

(epilepsy from .delta.- and .mu.-receptor agonists antagonism by)

IT 63631-40-3

RL: BIOL (Biological study)

(epilepsy induction by)

=>

L41 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2003 ACS
 AN 1990:400758 CAPLUS
 DN 113:758
 TI Naloxone-induced withdrawal syndrome after administration of selective opioid agonists or after activation of the endogenous enkephalinergic system
 AU Maldonado, Rafael; Waksman, Gilles; Feger, Jean; Roques, Bernard P.
 CS Lab. Pharmacol., Fac. Pharm., Paris, 75006, Fr.
 SO Progress in Clinical and Biological Research (1990), 328(Int. Narc. Res. Conf. (INRC) '89), 531-4
 CODEN: PCBRD2; ISSN: 0361-7742
 DT Journal
 LA English
 CC 2-5 (Mammalian Hormones)
 AB Chronic administration to rats of RB 38A, a complete inhibitor of enkephalin catabolism, produced a phys. dependence similar to that produced by a **.delta.-opioid** receptor agonist (DSTBULET), but less intense than that produced by the **.mu.-opioid** receptor agonist (DAGO), as measured by withdrawal signs after **naloxone**. Rats infused with RB 38B, a selective inhibitor of enkephalinase, exhibited a negligible abstinence syndrome after challenge with **naloxone**. Thus, after chronic activation of the endogenous enkephalinergic system, a withdrawal syndrome resembling that induced by **.delta.-opioid** chronic activation, but apparently less intense, is obsd.
 ST enkephalin opioid receptor **drug dependence**
 IT Enkephalins
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (metab. of, withdrawal syndrome after chronic inhibition of, **.delta.-opioid** receptors in relation to)
 IT **Drug dependence**
 (.delta.-opioid receptors mediation of, after chronic activation of endogenous enkephalinergic system)
 IT Enzymes
 RL: BIOL (Biological study)

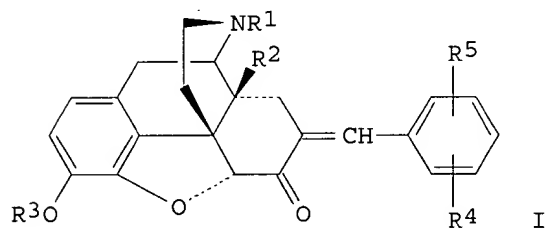
L41 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2003 ACS
 AN 1993:574119 CAPLUS
 DN 119:174119
 TI Involvement of .delta.-opioid receptors in physical dependence on butorphanol
 AU Jaw, Shyhwen P.; Hoskins, Beth; Ho, Ing K.
 CS Med. Cent., Univ. Mississippi, Jackson, MS, 39216, USA
 SO European Journal of Pharmacology (1993), 240(1), 67-72
 CODEN: EJPHAZ; ISSN: 0014-2999
 DT Journal
 LA English
 CC 1-11 (Pharmacology)
 AB Butorphanol, a synthetic agonist/antagonist, has been shown to act on .mu.-, .delta.- and .kappa.-opioid receptors. However, the relative involvement of opioid receptor subtypes in mediating butorphanol dependence is not known. In the present study, naltrindole, a .delta.-selective non-peptide antagonist, was administered intracerebroventricularly (i.c.v.) to mask supraspinal .delta.-opioid receptors before and during the induction of butorphanol dependence. Treatment with naltrindole (0.1, 1, or 10 nmol/5 .mu.L per rat) significantly blocked naloxone-, a nonspecific antagonist, pptd. butorphanol withdrawal behaviors (escape behavior, teeth-chattering, wet shakes, forepaw tremors, ptosis, diarrhea, body wt. loss, and hypothermia) at all doses tested, and decreased ejaculation at 0.1 nmol in butorphanol-infused rats. In contrast, naltrindole treatment had no effect on yawning, or urination. These results indicate that central .delta.-opioid receptors are involved in mediating butorphanol dependence in rats.
 ST butorphanol dependence delta opioid receptor
 IT **Drug dependence**
 (on butorphanol, .delta.-opioid receptors in)
 IT Opioids
 RL: BIOL (Biological study)
 (.delta.-, receptors, in butorphanol dependence)
 IT Receptors
 RL: BIOL (Biological study)

L41 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2003 ACS
 AN 1994:45817 CAPLUS
 DN 120:45817
 TI A nonpeptidic **delta opioid** receptor agonist, BW373U86,
 attenuates the development and expression of morphine abstinence
 precipitated by **naloxone** in rat
 AU Lee, Paul H. K.; McNutt, Robert W.; Chang, Kwen Jen
 CS Div. Cell Biol. Org. Chem., Burroughs Wellcome Co., Research Triangle
 Park, NC, USA
 SO Journal of Pharmacology and Experimental Therapeutics (1993), 267(2),
 983-7
 CODEN: JPETAB; ISSN: 0022-3565
 DT Journal
 LA English
 CC 1-11 (Pharmacology)
 AB The effect of (.+-.)-4-((.alpha.-R*)-.alpha.-((2S*, 5R*)-4-allyl-2,5-
 dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide (BW373U86),
 the first potent nonpeptidic, highly selective delta opioid receptor
 agonist, on morphine dependence was studied in rats. Continuous infusion
 of BW373U86 by a s.c. implanted osmotic minipump did not induce any
 abnormal behavior. After 6 days of BW373U86 infusion, i.p. injection of a
 high dose of naloxone or naltrindole did not ppt. morphine-like abstinence
 syndromes. Furthermore, a single injection of BW373U86 did not induce
 abstinence syndromes or modulate morphine abstinence pptd. by naloxone in
 chronic morphine-treated rats. However, naloxone-pptd. abstinence
 syndromes in morphine-dependent rats were partially suppressed by BW373U86
 in a dose-dependent manner when the compd. was infused s.c. before and
 throughout morphine treatment. Abstinence signs such as wet-dog shake,
 forelimb tremor and teeth chattering were either suppressed or the
 intensity was significantly attenuated in these BW373U86-infused rats.
 This effect was antagonized by naltrindole. These data show that chronic
 infusion of BW373U86 does not produce phys. dependence and that it
 attenuates some abstinence behaviors in morphine-dependent rats via delta
 opioid receptors.
 ST BW373U86 delta receptor agonist morphine withdrawal
 IT **Drug dependence**
 (on morphine, BW373U86 attenuation of abstinence syndrome in)
 IT Opioids
 RL: BIOL (Biological study)
 (.delta.-, BW373U86, attenuation of abstinence syndrome in morphine
 dependence by)
 IT 57-27-2, Morphine, biological studies
 RL: BIOL (Biological study)
 (dependence on, withdrawal from, BW373U86 attenuation of abstinence
 syndrome in)
 IT 150428-54-9, BW 373U86
 RL: BIOL (Biological study)
 (morphine withdrawal behavior attenuation by, as delta agonist)

L41 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2003 ACS
 AN 1994:245579 CAPLUS
 DN 120:245579
 TI Preparation of .delta.-opioid receptor-selective benzylidenemorphinans for treatment of alcohol abuse
 IN Portoghese, Philip S.
 PA University of Minnesota, USA
 SO PCT Int. Appl., 23 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM C07D489-02
 ICS A61K031-485; C07D489-08
 CC 31-3 (Alkaloids)
 Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9321188	A1	19931028	WO 1993-US3221	19930405
	W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9339457	A1	19931118	AU 1993-39457	19930405
	EP 638081	A1	19950215	EP 1993-908747	19930405
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 07505655	T2	19950622	JP 1993-518430	19930405
	US 6271239	B1	20010807	US 1995-440989	19950515
PRAI	US 1992-867997	A	19920413		
	WO 1993-US3221	A	19930405		
	US 1994-267844	B1	19940629		
OS	MARPAT 120:245579				
GI					



AB Title compds. I [R1 = alkyl, cycloalkylalkyl, cycloalkenylalkyl, etc.; R2 = H, OH, carboxyalkyl; R3 = H, alkyl, alkanoyl; R4, R5 = H, F, Cl, Br, NH2, NO2, alkyl, alkoxy; or R4R5 = benzo, methylenedioxy] and their pharmaceutically acceptable salts, effective in suppressing alc. consumption by humans, are prepd. E.g., a mixt. of **naltrexone** hydrochloride and benzaldehyde in MeOH contg. NaOMe was refrigerated for 14 h and then neutralized with HCl to give the title compd. 7-benzylidene-7-dehydronaltrexone, which showed a higher degree of binding at .delta.-opioid receptor than the std. .delta. agonist NTI.

ST delta opioid receptor antagonist; alcoholism treatment
benzylidenemorphinan

IT **Drug dependence**

Patent Assignment Abstract of Title

Total Assignments: 1

Application #: 09901362

Filing Dt: 07/09/2001

Patent #: NONE

Issue Dt:

PCT #: NONE

Publication #: NONE

Pub Dt:

Inventors: Stafford McLean, Stanton F. Mchardy, Spiros Liras

Title: Use of delta opioid receptor ligands and serotonin reuptake inhibitors in the treatment of chemical dependencies

Assignment: 1

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Assignors: MCLEAN, STAFFORD

Exec Dt: 08/08/2002

LIRAS, SPIROS

Exec Dt: 08/08/2002

MCHARDY, STANTON F.

Exec Dt: 08/08/2002

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Search Results as of: 3/25/2003 4:28:54 P.M.

(alcoholism, treatment of, .delta.-opioid receptor-selective
benzylidenemorphinans)

IT Opioids
RL: BIOL (Biological study)
(.delta.-, receptors, -selective benzylidenemorphinans, for treatment
of alc. abuse)

IT Receptors
RL: BIOL (Biological study)
(.delta.-opioid, -selective benzylidenemorphinans, for treatment of
alc. abuse)

IT 129468-28-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as opioid receptor antagonist)

IT 100-52-7, Benzaldehyde, reactions 16676-29-2, Naltrexone hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with benzaldehyde in prepn. of opioid receptor
antagonist)

L41 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2003 ACS
AN 1995:579616 CAPLUS
DN 122:307195
TI Chronic activation of inhibitory .delta.-opioid receptors cross-regulates the stimulatory adenylate cyclase-coupled prostaglandin E1 receptor system in neuroblastoma .times. glioma (NG108-15) hybrid cells
AU Ammer, Hermann; Schulz, Ruediger
CS Inst. Pharmacology, Toxicology Pharmacy, Univ. Munich, Munich, Germany
SO Journal of Neurochemistry (1995), 64(6), 2449-57
CODEN: JONRA9; ISSN: 0022-3042
PB Lippincott-Raven
DT Journal
LA English
CC 2-9 (Mammalian Hormones)
Section cross-reference(s): 1
AB The present article investigates chronic opioid regulation of the stimulatory adenylate cyclase-coupled prostaglandin E1 (PGE1) receptor system in neuroblastoma .times. glioma (NG108-15) hybrid cells. Persistent activation of .delta.-opioid receptors by morphine (10 .mu.mol/L; 3 days) substantially down-regulates the no. of PGE1 binding sites by .apprx.30%, without affecting their affinity. Radioligand binding studies performed in the presence of GTP.gamma.S (100 .mu.mol/L) further revealed that the remaining PGE1 binding sites are still capable of interacting functionally with their assocd. stimulatory G proteins, Gs. On the postreceptor level, neither changes in the abundance nor in the intrinsic activity of the .alpha. subunit of Gs (Gs.alpha.) were found during the state of opioid dependence, as has been verified by western blot and S49 cyc- reconstitution expts., resp. Evaluation of the functional interaction between PGE1 receptors and Gs by receptor-stimulated, cholera toxin-catalyzed ADP-ribosylation of Gs.alpha. revealed a significant increase in the ability of PGE1 receptors to activate Gs.alpha. (3.3-fold increase in EC50) in cells chronically exposed to morphine. This effect was completely blocked by coincubation of the cells together with the opiate antagonist **naloxone** (100 .mu.mol/L; 3 days), whereas pptn. of morphine withdrawal by **naloxone** (100 .mu.mol/L) had no further effect on sensitization in PGE1 receptor/Gs coupling. These findings provide evidence that the stimulatory adenylate cyclase-coupled PGE1 receptor system represents a potential target of chronic .delta.-opioid receptor activation in NG108-15 hybrid cells. They further suggest that sensitization in stimulatory signal transduction plays a crit. role in the generation of opioid dependence.
ST delta opioid receptor PGE1; Gs protein PGE1 receptor opioid
IT **Drug dependence**
Signal transduction, biological
(.delta.-opioid receptors cross-regulation of stimulatory adenylate cyclase-coupled PGE1 receptors in neuroblastoma .times. glioma hybrid cells)
IT Prostaglandin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.delta.-opioid receptors cross-regulation of stimulatory adenylate cyclase-coupled PGE1 receptors in neuroblastoma .times. glioma hybrid cells)
IT G proteins (guanine nucleotide-binding proteins)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Gs (adenylate cyclase-stimulating), .alpha.-subunit; .delta.-opioid receptors cross-regulation of stimulatory adenylate cyclase-coupled PGE1 receptors in neuroblastoma .times. glioma hybrid cells)
IT Neuroglia
(neoplasm, .delta.-opioid receptors cross-regulation of stimulatory adenylate cyclase-coupled PGE1 receptors in neuroblastoma .times.

glioma hybrid cells)

L41 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2003 ACS
 AN 1995:818233 CAPLUS
 DN 123:218314
 TI Effect of naltrindole on the development of physical dependence on morphine in mice: a behavioral and biochemical study
 AU Suzuki, Tsutomu; Tsuji, Minoru; Mori, Tomohisa; Misawa, Miwa; Nagase, Hiroshi
 CS Department Pharmacology, School Pharmacy, Hoshi University, Tokyo, 142, Japan
 SO Life Sciences (1995), 57(17), PL247-PL252
 CODEN: LIFSAK; ISSN: 0024-3205
 PB Elsevier
 DT Journal
 LA English
 CC 1-11 (Pharmacology)
 AB The effect of pretreatment with the **.delta. opioid** receptor antagonist naltrindole (NTI) on the development of phys. dependence on morphine was investigated in mice. Several withdrawal signs, an increase in cortical noradrenaline turnover and a decrease in dopamine turnover in the limbic forebrain were obsd. following **naloxone** challenge in morphine-dependent mice. Pretreatment with NTI (0.35-mg/kg, s.c.) during chronic morphine treatment dose-dependently suppressed the behavioral and biochem. changes after withdrawal. The blocking effects of NTI suggest that **.delta. opioid** receptors may play a significant role in modulating the development of phys. dependence on morphine.
 ST morphine dependence brain delta opioid receptor
 IT **Drug dependence**
 (morphine **dependence** modulation by brain **.delta.-opioid** receptors)
 IT Behavior
 (withdrawal; morphine dependence modulation by brain **.delta.-opioid** receptors in relation to)
 IT Brain
 (cerebral cortex, morphine dependence modulation by **.delta.-opioid** receptors in)
 IT Brain
 (prosencephalon, morphine dependence modulation by **.delta.-opioid** receptors in)
 IT Opioid receptors
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (.delta.-, morphine dependence modulation by brain **.delta.-opioid** receptors)
 IT Receptors
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (.delta.-opioid, morphine dependence modulation by brain **.delta.-opioid** receptors)
 IT 57-27-2, Morphine, biological studies
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (dependence on morphine modulation by brain **.delta.-opioid** receptors)
 IT 51-41-2, Noradrenaline 51-61-6, Dopamine, biological studies
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (morphine dependence effect on brain dopamine and noradrenaline turnover in relation to **.delta.-opioid** receptors)
 IT 102-32-9, DOPAC 306-08-1, Homovanillic acid 534-82-7, 3-Methoxy-4-hydroxyphenylethylene glycol
 RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
 (morphine dependence effect on brain dopamine and noradrenaline

turnover in relation to .delta.-opioid receptors)
IT 111555-53-4, Naltrindole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(morphine dependence response to)

L41 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2003 ACS
 AN 1995:922695 CAPLUS
 DN 124:21606
 TI Attenuation of morphine tolerance and dependence with the highly selective
 .delta.-opioid receptor antagonist TIPP[.psi.]
 AU Fundytus, Marian E.; Schiller, Peter W.; Shapiro, Michelle; Weltrowska,
 Grazyna; Coderre, Terence J.
 CS Pain Mechanisms Laboratory, Clinical Research Institute of Montreal,
 Montreal, Quebec, Can.
 SO European Journal of Pharmacology (1995), 286(1), 105-8
 CODEN: EJPHAZ; ISSN: 0014-2999
 PB Elsevier
 DT Journal
 LA English
 CC 1-11 (Pharmacology)
 AB We examd. the effects of i.c.v. treatment with naltrindole, and the two
 highly selective peptide .delta.-opioid receptor
 antagonists H-Tyr-Tic-Phe-Phe-OH (TIPP) and H-Tyr-Tic.psi.[CH2-NH]-Phe-Phe-
 OH (TIPP[.psi.]), on the development of morphine tolerance and dependence.
 Each treatment significantly decreased **naloxone**-pptd.
 withdrawal, with TIPP[.psi.] reducing the most symptoms. TIPP[.psi.], but
 neither naltrindole nor TIPP, attenuated the development of analgesic
 tolerance in the tail-flick test. These results suggest that
 .delta.-opioid receptors are critically involved in the development of
 morphine tolerance and dependence.
 ST morphine tolerance dependence delta opioid receptor
 IT **Drug dependence**
 Drug tolerance
 (.delta.-opioid receptors in development of morphine tolerance and
 dependence)
 IT Opioid receptors
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (.delta.-, .delta.-opioid receptors in development of morphine
 tolerance and dependence)
 IT Receptors
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (.delta.-opioid, .delta.-opioid receptors in development of morphine
 tolerance and dependence)
 IT 57-27-2, Morphine, biological studies
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or
 effector, except adverse); BSU (Biological study, unclassified); THU
 (Therapeutic use); BIOL (Biological study); USES (Uses)
 (.delta.-opioid receptors in development of morphine tolerance and
 dependence)

L41 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2003 ACS
 AN 1995:976186 CAPLUS
 DN 124:76236
 TI Agonist regulation of the expression of the delta opioid receptor in NG108-15 cells
 AU Kim, Dong Sun; Chin, Hemin; Klee, Werner A.
 CS Laboratory of Molecular Biology, NIMH, Bldg. 36, Rm. 1B08, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD, 20892, USA
 SO FEBS Letters (1995), 376(1,2), 11-14
 CODEN: FEBLAL; ISSN: 0014-5793
 PB Elsevier
 DT Journal
 LA English
 CC 1-11 (Pharmacology)
 AB Exposure of neuronal cells to the chronic presence of opiates leads to a complex series of biochem. events which reflect the changes that result in tolerance and dependence in animals. To achieve a better understanding of the mol. mechanisms underlying these processes, the authors have examd. the effect of agonist efficacy on the regulation of the .delta.-opioid receptor mRNA in NG108-15 cells. Incubation with various opiates decreased receptor nos. in the order of their efficacy. Northern blot anal. showed that there are 4 size classes of mRNA coding for the .delta.-opioid receptor in NG108-15 cells even though only one known protein species is found. Moreover, the amt. of each transcript is coordinately decreased by long-term etorphine treatment, but not necessarily to the same extent. The etorphine-induced decrease in receptor mRNA was slow in onset, whereas a much more rapid loss of receptor no. was obsd. This disparity suggests that the down-regulation induced by etorphine can occur both at the levels of receptor protein modification and receptor gene expression, and that the mechanisms of the two processes may be different.
 ST delta opioid receptor gene regulation agonist
 IT **Drug dependence**
 Drug tolerance
 (agonist regulation of gene expression of delta opioid receptor in NG108-15 cells in relation to tolerance and dependence)
 IT Opioids
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (agonist regulation of gene expression of delta opioid receptor in NG108-15 cells in relation to tolerance and dependence)
 IT Gene, animal
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (.delta.-opioid receptor-encoding; agonist regulation of gene expression of delta opioid receptor in NG108-15 cells in relation to tolerance and dependence)
 IT Opioid receptors
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (.delta.-, agonist regulation of gene expression of delta opioid receptor in NG108-15 cells in relation to tolerance and dependence)
 IT Receptors
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (.delta.-opioid, agonist regulation of gene expression of delta opioid receptor in NG108-15 cells in relation to tolerance and dependence)
 IT 57-27-2, Morphine, biological studies 62-67-9, **Nalorphine** 14357-78-9, **Diprenorphine** 14521-96-1, Etorphine
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (agonist regulation of gene expression of **delta opioid** receptor in NG108-15 cells in relation to tolerance and dependence)

L41 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2003 ACS

AN 1996:234775 CAPLUS

DN 124:307335

TI Role of δ -opioid receptors in mediating the aversive stimulus effects of morphine withdrawal in the rat

AU Funada, Masahiko; Schutz, Christian G.; Shippenberg, Toni S.

CS Clinical Pharmacology Branch, Division of Intramural Research, National Institute on Drug Abuse, National Institute of Health, P.O. Box 5180, Baltimore, MD, 21224, USA

SO European Journal of Pharmacology (1996), 300(1/2), 17-24

CODEN: EJPHAZ; ISSN: 0014-2999

PB Elsevier

DT Journal

LA English

CC 1-11 (Pharmacology)

AB An unbiased place preference conditioning procedure was used to examine the role of δ -opioid receptors in mediating the aversive effects of opioid withdrawal. Rats were implanted s.c. with two pellets each contg. placebo or 75 mg morphine. Single-trial conditioning sessions with saline and the opioid receptor antagonists naloxone (0.001-1.0 mg/kg, s.c.), naltrindole (0.01-3.0 mg/kg, s.c.) or naltriben (0.01-3.0 mg/kg, s.c.) commenced 4 days later. During these conditioning sessions, phys. signs of withdrawal were also quantified. Tests of conditioning were conducted on day 5. Naloxone in doses of 0.01-1.0 mg/kg produced significant conditioned place aversions in morphine-implanted animals. A dose of 0.01 mg/kg produced few phys. withdrawal signs whereas higher doses resulted in marked wet dog shakes, body wt. loss, ptosis and diarrhea. No such effects were obsd. in control (placebo-implanted) animals. Administration of the selective δ -opioid receptor antagonists naltrindole and naltriben produced dose-related place aversions in morphine-implanted animals. The magnitude of these effects did not differ from that obsd. with naloxone. The min. EDs of naltrindole and naltriben were 0.1 mg/kg. Doses of 0.1-1.0 mg/kg produced few, if any, somatic signs of withdrawal whereas higher doses of these antagonists only produced diarrhea and wet-dog shakes. Other withdrawal signs were absent. In contrast to the opioid receptor antagonists tested, the dopamine D1 receptor antagonist SCH23390 failed to produced conditioned place aversions or phys. signs of withdrawal in morphine-pelleted animals. These data demonstrate that the selective blockade of either δ - or μ -opioid receptors is sufficient to induce conditioned aversive effects in morphine-dependent animals. They also indicate that phys. symptoms assocd. with pptd. morphine withdrawal differ depending upon the opioid receptor antagonist employed.

ST morphine dependence withdrawal delta opioid receptor

IT **Drug dependence**

(role of δ -opioid receptors in mediating the aversive stimulus effects of morphine withdrawal in the rat)

IT Opioid receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(δ -, role of δ -opioid receptors in mediating the aversive stimulus effects of morphine withdrawal in the rat)

IT Receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(δ -opioid, role of δ -opioid receptors in mediating the aversive stimulus effects of morphine withdrawal in the rat)

IT Opioid receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(μ -, selective blockade of either δ - or μ -opioid receptors is sufficient to induce conditioned aversive effects in morphine-depen

L41 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2003 ACS
 AN 1999:375048 CAPLUS
 DN 131:139416
 TI Further studies on the involvement of the arachidonic acid cascade in the acute dependence produced by .mu., .kappa. and .delta. opioid agonists in isolated tissues
 AU Capasso, Anna
 CS Department of Pharmaceutical Sciences, University of Salerno, Salerno, 84084, Italy
 SO Neuropharmacology (1999), 38(6), 871-877
 CODEN: NEPHBW; ISSN: 0028-3908
 PB Elsevier Science Ltd.
 DT Journal
 LA English
 CC 1-11 (Pharmacology)
 AB The effects of phospholipase A2, cyclooxygenase-1, cyclooxygenase-2, and 5-lipoxygenase inhibitors on acute opiate withdrawal induced by selective .mu., .kappa. and .delta. receptor agonists was investigated in vitro. After a 4 min in vitro exposure to (D-Ala2-N-methyl-Phe-Gly5-ol)enkephalin (DAMGO; a highly selective .mu. agonist) and trans(.+-.)-3,4-dichloro-N-methyl-N-(2-(1-pyrrolidinyl)cyclohexyl)benzeneacetamide (U50-488H; a highly selective .kappa. agonist) a strong contraction of the guinea pig isolated ileum was obsd. after the addn. of naloxone. This effect was also obsd. when rabbit isolated jejunum was pretreated with deltorphin (a highly selective .delta. agonist). Mepacrine (a phospholipase A2 inhibitor), tolmetin (a selective cyclooxygenase-1 inhibitor) and meloxicam (a selective cyclooxygenase-2 inhibitor) treatment before or after DAMGO or U50-488H were able to both prevent and reverse the naloxone-induced contraction after exposure to the opioid agonists, in a concn.-dependent fashion. In addn., nordihydroguaiaretic acid (a 5-lipoxygenase inhibitor) was able to block the naloxone-induced contraction following exposure to DAMGO or U50-488H if injected either before or after the opioid agonist. In contrast, mepacrine, tolmetin, meloxicam and nordihydroguaiaretic acid did not affect the **naloxone**-induced contraction after exposure to deltorphin. The results of the present study confirm and extend a previous study performed with morphine indicating that arachidonic acid and its metabolites (prostaglandins and leukotrienes) are involved in the development of opioid withdrawal induced by selective .mu. and .kappa. opioid agonists whereas no effects were obsd. on withdrawal induced by the selective .**delta. opioid** agonist deltorphin.
 ST opioid agonist dependence withdrawal arachidonate cascade
 IT **Drug dependence**
 Drug withdrawal
 (involvement of arachidonic acid cascade in acute dependence produced by .mu., .kappa. and .delta. opioid agonists in isolated tissues)
 IT Leukotrienes
 Prostaglandins
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (involvement of arachidonic acid cascade in acute dependence produced by .mu., .kappa. and .delta. opioid agonists in isolated tissues)
 IT Opioids
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (.kappa.-; involvement of arachidonic acid cascade in acute dependence produced by .mu., .kappa. and .delta. opioid agonists in isolated tissues)
 IT Opioids
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (.delta.-; involvement of arachidonic acid cascade in acute dependence produced by .mu., .kappa. and .delta. opioid agonists in isolated tissues)

IT Opioids
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (.mu.-; involvement of arachidonic acid cascade in acute dependence produced by .mu., .kappa. and .delta. opioid agonists in isolated tissues)

IT 39391-18-9, Cyclooxygenase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (1 and 2, inhibitors; involvement of arachidonic acid cascade in acute dependence produced by .mu., .kappa. and .delta. opioid agonists in isolated tissues)

IT 9001-84-7, Phospholipase A2 80619-02-9, 5-Lipoxygenase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (inhibitors; involvement of arachidonic acid cascade in acute dependence produced by .mu., .kappa. and .delta. opioid agonists in isolated tissues)

IT 83-89-6, Mepacrine 500-38-9, Nordihydroguaiaretic acid 26171-23-3, Tolmetin 71125-38-7, Meloxicam 78123-71-4, DAMGO 83913-06-8 182441-20-9, Deltorpin
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (involvement of arachidonic acid cascade in acute dependence produced by .mu., .kappa. and .delta. opioid agonists in isolated tissues)

IT 506-32-1, Arachidonic acid
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (involvement of arachidonic acid cascade in acute dependence produced by .mu., .kappa. and .delta. opioid agonists in isolated tissues)

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L2          1 FILE CAPLUS
TOTAL FOR ALL FILES
L3          2 S US6444679/PN
           SELECT L1 1 RN
L4          1 FILE USPATFULL
L5          1 FILE CAPLUS
TOTAL FOR ALL FILES
L6          2 S E8-E85
L7          290 FILE USPATFULL
L8          3826 FILE CAPLUS
TOTAL FOR ALL FILES
L9          4116 S (DELTA OPIOID) OR (DELTA-OPIOID) OR (.DELTA.OPIOID)
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L11         13075 FILE CAPLUS
TOTAL FOR ALL FILES
L12         14833 S (SUBSTANCE OR CHEMICAL OR DRUG) (3A) (DEPENDENC?)
L13          31 FILE USPATFULL
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TOTAL FOR ALL FILES
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L16          7 FILE USPATFULL
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TOTAL FOR ALL FILES
L18          8 S L15 AND SEROTONIN AND COMBIN?
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TOTAL FOR ALL FILES
L21        1801 S SERTRALINE
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TOTAL FOR ALL FILES
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L25          5 FILE USPATFULL
L26          1 FILE CAPLUS
TOTAL FOR ALL FILES
L27          6 S L21 AND L9
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TOTAL FOR ALL FILES
L30        23109 S NALOXONE OR NALTREXONE OR CYCLOZZOCINE OR DIPRENORPHINE OR ET
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TOTAL FOR ALL FILES
L33         575 S L30 (1S) L9
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L40          6 FILE USPATFULL
L41         23 FILE CAPLUS
TOTAL FOR ALL FILES
L42         29 S L33 AND L12
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L60 ANSWER 38 OF 46 CAPLUS COPYRIGHT 2003 ACS

AB [3H]bremazocine (5 nM), in the presence of excess unlabeled .mu. and .delta. opioid ligands labeled two anatomically distinct populations of binding sites in the bovine adrenal medulla; a high d. over the peripheral adrenaline-contg. region of the medulla and a lower d. over the central noradrenaline-contg. region. This non-.mu., non-.delta. opioid binding was specific (diprenorphine sensitive) but did not appear to involve classical .kappa. (.kappa.1), .sigma. or PCP binding sites being insensitive to high concns. of dynorphin (1-13), 3-PPP or MK-801. A significant proportion of the binding at both locations was however sensitive to competition by U50,488H or metorphamide. These data provide further evidence to support the existence of multiple opioid binding sites in the bovine adrenal medulla.

AN 1991:465283 CAPLUS

DN 115:65283

L60 ANSWER 39 OF 46 CAPLUS COPYRIGHT 2003 ACS

AB In previous studies, it was demonstrated that chronic treatment of rats with either etorphine or [D-Ala2,D-Leu5]-enkephalin (DADLE) resulted in the redn. of opioid receptor binding activities during the course of tolerance development. In both cases, .mu.-opioid receptor binding capacity was attenuated together with the .delta.-opioid receptor binding capacity. Because both etorphine and DADLE are relatively non-specific opioid ligands, interacting with both .mu. and .delta. receptors, these studies could not det. whether down-regulation of a specific receptor type is possible. Therefore, in the current studies, rats were rendered tolerant to the .mu.-opioid receptor-selective ligand PL 017 and the receptor binding capacity was measured afterwards. Treating Sprague-Dawley rats with increasing doses of PL 017 (2.5-20 .mu.g/kg) intracerebroventricularly for 5 days resulted in a 30-40-fold increase in the AD50 of the peptide to elicit the antinociceptive response and about a 14-fold increase in the ED50 of the peptide to elicit the catatonic effect. When .mu.-and .delta.-binding was detd. using [3H]diprenorphine in the presence of morphiceptin or [D-Pen2,D-Pen5]-enkephalin (DPDPE), resp., a decrease (20-30%) in the .mu.-opioid receptor binding, but not in .delta.-opioid receptor binding, was obsd. in all the brain areas tested after 5 days of PL 017 treatment. Scatchard anal. of the [3H]Tyr-D-Ala-Gly-MePhe-Gly-ol ([3H]DAMGO) satn. binding data revealed a decrease in Bmax values and no change in the Kd values. Hence, .mu.-opioid receptors can be specifically regulated by ligand in the brain as .delta.-receptors are in neuroblastoma .times. glioma NG 108-15 cells. Chronic activation of the .mu.-opioid receptor in the brain would result in the down-regulation of the binding sites.

AN 1990:585043 CAPLUS

DN 113:185043

L60 ANSWER 40 OF 46 CAPLUS COPYRIGHT 2003 ACS

AB Previous studies about the differential effect of chronic membrane depolarization on the expression of .mu. and .delta. opioid receptors prompted the investigation of whether the same treatment also regulates the expression of .kappa. opioid receptors. Embryonic guinea pig brain cells that exhibit in culture a high d. of .kappa. receptors were treated for different time periods with KCl, and the no. of these receptors was detd. with the universal opioid ligand [3H]diprenorphine. In a second set of expts. the cultures were treated with the Na channel activator veratridine and opioid receptors were detd. with the selective .kappa. ligand [3H]U 69,593. The results indicate that chronic membrane depolarization (for 3 or 6 days) decreases the no. of .kappa. receptors, with no effect on the affinity of the ligands. Taken together with previous reports, it is suggested that neuronal activation has a selective and possibly opposite regulatory role

on the expression of the 3 opioid receptors.

AN 1990:192268 CAPLUS

DN 112:192268

L60 ANSWER 41 OF 46 CAPLUS COPYRIGHT 2003 ACS

AB Chronic treatment of rats with [D-Ala²,D-Leu⁵]enkephalin (DADLE) resulted in the development of tolerance to the antinociceptive effect of this opioid peptide. When opioid receptor binding was measured, time-dependent decreases in [3H]diprenorphine binding to the P2 membranes prepd. from the cortex, midbrain, and striatum were obsd. Scatchard anal. of the satn. binding data revealed a decrease in Bmax values and no change in the Kd values of [3H]diprenorphine binding to these brain regions, indicative of down-regulation of the receptor. This redn. in the opioid receptor binding activities could be demonstrated to be due to the DADLE effect on the .delta.-opioid receptors in these brain regions. When [3H]DADLE binding was carried out in the presence of morphiceptin, a significant redn. of the .delta.-opioid receptor binding was obsd. in all brain areas tested. .mu.-Opioid receptor binding decrease was obsd. only in the striatum after 5 days of DADLE treatment. Addnl., the onset of .delta.-opioid receptor decrease in the midbrain area was rapid, within 6 h of the initiation of the chronic DADLE treatment. Thus, analogous to previous observations in which chronic etorphine treatment preferentially reduced .mu.-opioid receptor binding, chronic DADLE treatment preferentially reduced .delta.-opioid receptor binding activity.

AN 1988:605217 CAPLUS

DN 109:205217

L60 ANSWER 42 OF 46 CAPLUS COPYRIGHT 2003 ACS

AB Multiple affinity states of opioid receptors of the .mu. and .delta. types were identified in membranes prepd. from cells which bear only 1 type of opioid receptor (.mu. receptors in 7315c cells and .delta. receptors in NG 108-15 cells) and in guinea pig cortical membranes where both types of receptors were present in the membrane preps. The states of .mu. and .delta. receptors which have agonist affinities too low to be identified by radiolabeled agonist were measured indirectly by agonist competition for sites labeled by radioactive antagonist. By using analogs of guanyl nucleotides, the competition of the .mu. and .delta. agonists Tyr-D-Ala-Gly-(Me)Phe-Gly-ol (DAGO) and [D-Ser²,Leu⁵]enkephalin-Thr (DSLET) against [3H]diprenorphine ([3H]DIP) or [3H]naloxone ([3H]NAL) binding to opioid receptors was examd. and identified several agonist affinity states. In the absence of added nucleotide, competition of DSLET for [3H]DIP binding to .delta. opioid receptors revealed the presence of 2 binding sites with differing apparent agonist affinities. Addn. of guanosine 5'-O-(2-thiodiphosphate) (GDP.beta.S) produced a steep monophasic curve which was best fit by a 1-site model. In contrast, in the presence of added GTP or guanosine 5'-O-(3-thiotriphosphate) (GTP.gamma.S), 2 affinity states were again apparent for DSLET competition at the .delta. receptor. The competition curve with GTP was shifted to the right relative to that produced in the absence of added guanyl nucleotide, indicating the presence of a lower apparent affinity state than any obsd. under other treatment conditions. DAGO competed against [3H]DIP or [3H]NAL binding to .mu. receptors over a wide concn. range in the absence of added guanyl nucleotide, consistent with the occupation by this ligand of >1 agonist affinity state of the .mu. receptor. However, when GDP.beta.S was added to the incubation mixt., only a single binding site was identified. Two .mu. receptor affinity states were again obsd. in the presence of added GTP or GTP.gamma.S. One of these had a significantly lower apparent affinity than did those states detected in the absence of added nucleotide or with GDP.beta.S. Pertussis toxin treatment resulted in a monophasic agonist competition curve which was best fitted by a single-site model in both 7315c and NG108-15 cell membranes. Addn. of 100 .mu.M GTP did not affect the agonist apparent dissocn. const. or maximal binding capacity after

pertussis toxin treatment, suggesting that sites labeled under these conditions were not functionally assocd. with a G protein. In general, the effects of guanyl nucleotides were qual. similar at .mu. and .delta. receptors. The multiple apparent affinity states of each type of receptor probably reflect the preferential occurrence of different forms of agonist-receptor-G protein-guanyl nucleotide complex depending on the agonist or antagonist properties of the ligand and the guanyl nucleotides present.

AN 1988:401064 CAPLUS

DN 109:1064

L60 ANSWER 43 OF 46 CAPLUS COPYRIGHT 2003 ACS

AB Two monoclonal anti-idiotypic antibodies (anti-Id-135 and anti-Id-14, both of the IgM class) which interact with the binding site of opioid receptors were generated. A monoclonal anti-.beta.-endorphin antibody (3-E7) which displays binding characteristics for opioid ligands similar to opioid receptors served as the antigen and the hybridomas obtained were screened for anti-idiotypic antibodies with Fab fragments of 3-E7. The anti-idiotypes were then screened for opioid binding to rat brain membrane receptors, yielding several pos. clones, 2 of which were more intensively studied. Both anti-idiotypic antibodies were about equally potent in displacing the .mu.- and .delta.-opioid receptor ligands [3H]dihydromorphine, 125I-labeled .beta.-endorphin, [L-Ala2,D-Leu5-3H]enkephalin, and [3H]naloxone from rat brain membrane opioid receptors; no interaction was obsd. with the .kappa.-ligands [3H]ethylketazocine or [3H]bremazocine. The anti-idiotypic antibodies were able to ppt. [3H]diprenorphine binding sites from solubilized opioid receptor preps. In addn., both antibodies showed opioid antagonistic properties as demonstrated by their abilities to block the inhibitory effect of [D-Ala2,D-Leu5-3H]enkephalin on prostaglandin E1-stimulated cAMP accumulation in NG 108-15 hybrid cells. The findings demonstrate the successful generation of monoclonal antibodies interacting with membrane-bound and solubilized opioid receptors of the .mu.- and .delta.-type.

AN 1988:202919 CAPLUS

DN 108:202919

L60 ANSWER 44 OF 46 CAPLUS COPYRIGHT 2003 ACS

AB The modulatory effect of continued activation of opiate receptors with agonist on the receptor level was examd. in current studies. Rats were rendered tolerant to etorphine [14521-96-1] by s.c. implantation of osmotic minipumps contg. 3 mg/mL of etorphine for up to 7 days. During this period, there were a time-dependent increase in the AD50 values of etorphine to inhibit the tail-flick response and an increase in naloxone [465-65-6]-pptd. withdrawal signs. When these animals and others were sacrificed and the opiate receptor binding properties were examd., it could be demonstrated that there was also a time-dependent decrease in the amt. of [3H]diprenorphine specifically bound, with maximal attenuation reached 3 days after implantation. There was no alteration in .alpha.-2 adrenergic receptor binding. This obsd. decrease in [3H]diprenorphine binding was not due to the presence of nonwashed etorphine in the membrane, for acute administration of the same dose of etorphine before sacrificing did not produce an attenuation of the opiate receptor binding. Further examn. of opiate receptor binding in the brain regions of cortex, midbrain and striatum revealed the greatest decrease in the amt. of [3H]diprenorphine bound in striatal region after chronic etorphine treatment, a 68% decrease. When the relative decrease in .mu. and .delta. opioid receptor binding was detd. by carrying out [3H]-D-Ala2, DLeu5-enkephalin binding in the presence of 1 .mu.M morphiceptin, it was obsd. that, 3 days after etorphine treatment, there was a decrease in .mu.-opioid receptor binding, with minimal change in .delta.-opioid receptor binding in both brain regions of striatum and midbrain. Only in cortex was a decrease in binding of both receptor subtypes obsd. This decrease in binding of both receptor

subtypes obsd. This decrease in opiate receptor binding after chronic etorphine treatment was due to the decrease in Bmax values and not in the Kd values, as in the case of nonwashed membrane contg. etorphine. Also, an apparent increase in the affinity of [3H]diprenorphine was obsd. during chronic opiate treatment. These obsd. alterations in opiate receptor binding were opioid dependent, for chronic treatment of animals with either morphine [57-27-2] or naloxone produced an increase rather than a decrease in receptor binding. Chronic etorphine treatment did not alter the maximal inhibitory level of opiate regulation of adenylate cyclase [9012-42-4] in the striatum, but a 2.2-fold increase in D-Ala2, D-Leu5-enkephalin ID50 value was obsd. after 5 days of etorphine treatment. Therefore, in addn. to the obsd. .delta. opioid receptor down-regulation in clonal cell lines, chronic activation of the opiate receptor in brain with etorphine produced an apparent down-regulation of both the .mu.- and .delta.-opioid receptors.

AN 1987:207570 CAPLUS
DN 106:207570

L60 ANSWER 45 OF 46 CAPLUS COPYRIGHT 2003 ACS

AB The ability of ICI 174864 to displace 3H-labeled [D-Ala2,D-Leu5]enkephalin [63631-40-3] bound to the rat brain **.delta.-opioid** site was increased 8-16 fold by addn. of 25 mM NaCl. A smaller shift was obsd. for ICI 154129, but no shift was seen with either naloxone or **diprenorphine**. The results stress the importance of using the correct medium for binding assays, and suggest that the changes in .delta.-receptor conformation induced by Na+ also increase peptide antagonist binding.

AN 1986:180415 CAPLUS
DN 104:180415

L60 ANSWER 46 OF 46 CAPLUS COPYRIGHT 2003 ACS

AB The development of tolerance to opioid-induced alterations in intestinal ion transport processes was examd. Osmotic minipumps continuously delivering the prototypic .delta.-opioid agonist [D-Ala2,D-Leu5]-enkephalin (DADLE) [63631-40-3] (5 .mu.g/h) or the potent .mu.-opiate agonist fentanyl [437-38-7] (10 .mu.g/h) over 5 days were implanted s.c. into guinea pigs; control animals did not receive chronic drug infusions. DADLE, DADLE ethylamide [67787-85-3], and [D-Ala2,D-Met5]-enkephalin [64963-09-3] dose-dependently decreased base-line transepithelial p.d. and short-circuit current in isolated segments of ileal mucosa from untreated control animals, with an order of potency of DADLE > [D-Ala2,D-Met5]-enkephalin > DADLE ethylamide. In tissues from DADLE-infused animals, the antisecretory dose-effect curves of the 3 enkephalin analogs displayed downward shifts to the right compared to control conditions. In contrast, the potency of DADLE was increased in tissues from animals chronically infused with and rendered phys. dependent on fentanyl. The administration of the opioid antagonists naloxone, **diprenorphine**, or the selective **.delta.-opioid** antagonist M 154129 produced no changes in short-circuit current of mucosal segments from either DADLE- or fentanyl-infused animals. Chronic administration of either DADLE or fentanyl did not alter the effects of nonopioids, bombesin, somatostatin, or epinephrine on ion transport; however, the efficacy but not the potency of neurotensin [39379-15-2] in increasing short-circuit current was attenuated after chronic DADLE infusion. Apparently, tolerance without dependence selectively develops to the antisecretory effects of the enkephalins in the guinea pig ileal mucosa.

AN 1985:432504 CAPLUS
DN 103:32504

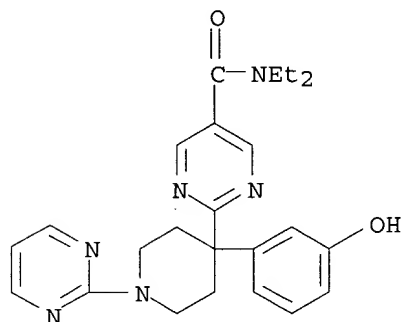
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L75 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 291753-99-6 REGISTRY
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FS 3D CONCORD
MF C24 H28 N6 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



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1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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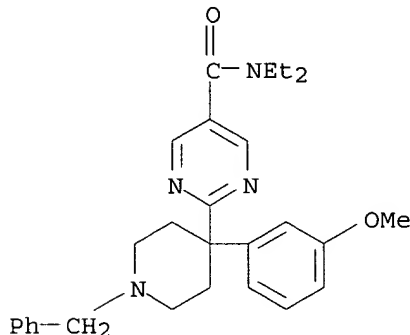
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RN 291753-76-9 REGISTRY
CN 5-Pyrimidinecarboxamide, N,N-diethyl-2-[4-(3-methoxyphenyl)-1-(phenylmethyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C28 H34 N4 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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NOTICE SET TO OFF FOR DISPLAY COMMAND
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DICTIONARY FILE UPDATES: 25 MAR 2003 HIGHEST RN 500688-79-9

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> S 291753-92-9/RN

L77 1 291753-92-9/RN

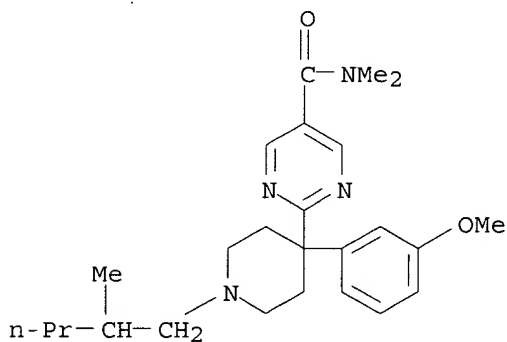
=> SET NOTICE 1 DISPLAY

NOTICE SET TO 1 U.S. DOLLAR FOR DISPLAY COMMAND
SET COMMAND COMPLETED

=> D L77 SQIDE 1-

YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):y
THE ESTIMATED COST FOR THIS REQUEST IS 5.63 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:y

L77 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 291753-92-9 REGISTRY
CN 5-Pyrimidinecarboxamide, 2-[4-(3-methoxyphenyl)-1-(2-methylpentyl)-4-piperidinyl]-N,N-dimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C25 H36 N4 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

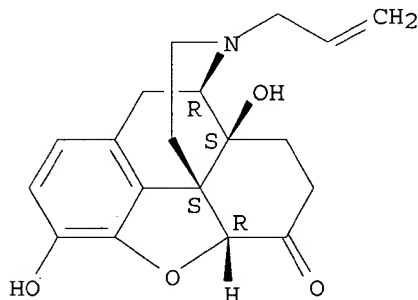
=> SET NOTICE LOGIN DISPLAY

NOTICE SET TO OFF FOR DISPLAY COMMAND
SET COMMAND COMPLETED

=>

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
 RN 465-65-6 REGISTRY
 CN Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5.alpha.)-(9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Morphinan-6-one, 17-allyl-4,5.alpha.-epoxy-3,14-dihydroxy- (8CI)
 CN Normorphinone, N-allyl-7,8-dihydro-14-hydroxy- (7CI)
 OTHER NAMES:
 CN (-)-Naloxone
 CN 12-Allyl-7,7a,8,9-tetrahydro-3,7a-dihydroxy-4aH-8,9c-iminoethanophenanthro[4,5-bcd]furan-5(6H)-one
 CN 1-Naloxone
 CN **Naloxone**
 FS STEREOSEARCH
 DR 5592-87-0
 MF C19 H21 N O4
 CI COM
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



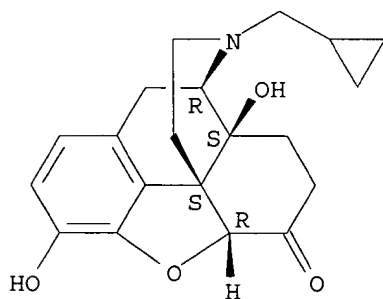
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4760 REFERENCES IN FILE CA (1962 TO DATE)
 23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 4767 REFERENCES IN FILE CAPLUS (1962 TO DATE)
 10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
 RN 16590-41-3 REGISTRY
 CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-,
 (5.alpha.)- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5.alpha.-epoxy-3,14-dihydroxy-
 (8CI)
 OTHER NAMES:
 CN 1-N-Cyclopropylmethyl-7,8-dihydro-14-hydroxynormorphinone
 CN Depotrex
 CN EN 1639
 CN N-Cyclopropylmethylnoroxymorphone
 CN **Naltrexone**
 CN Nemexin
 CN ReVia
 CN UM 792
 FS STEREOSEARCH
 MF C20 H23 N O4
 CI COM
 LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*,
 BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT,
 CBNB, CEN, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL,
 DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA,
 MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, RTECS*, SPECINFO, SYNTHLINE,
 TOXCENTER, USAN, USPAT2, USPATFULL, VETU
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



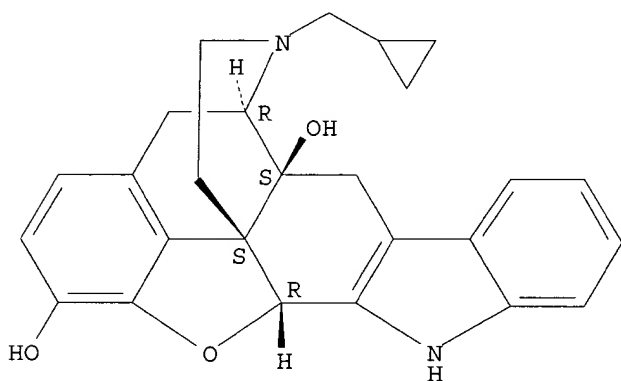
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1598 REFERENCES IN FILE CA (1962 TO DATE)
 36 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 1599 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=>

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
 RN 111555-53-4 REGISTRY
 CN 4,8-Methanobenzofuro[2,3-a]pyrido[4,3-b]carbazole-1,8a(9H)-diol,
 7-(cyclopropylmethyl)-5,6,7,8,14,14b-hexahydro-, (4bS,8R,8aS,14bR) - (9CI)
 (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN 4,8-Methanobenzofuro[2,3-a]pyrido[4,3-b]carbazole-1,8a(9H)-diol,
 7-(cyclopropylmethyl)-5,6,7,8,14,14b-hexahydro-, [8R-
 (4bS*,8.alpha.,8a.beta.,14b.beta.)]-
 OTHER NAMES:
 CN **Naltrindole**
 CN NIH 10589
 FS STEREOSEARCH
 MF C26 H26 N2 O3
 CI COM
 SR CA
 LC STN Files: ADISNEWS, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA,
 CANCERLIT, CAPLUS, CASREACT, DDFU, DRUGU, EMBASE, IPA, MEDLINE,
 TOXCENTER, USPAT2, USPATFULL
 (*File contains numerically searchable property data)

Absolute stereochemistry.



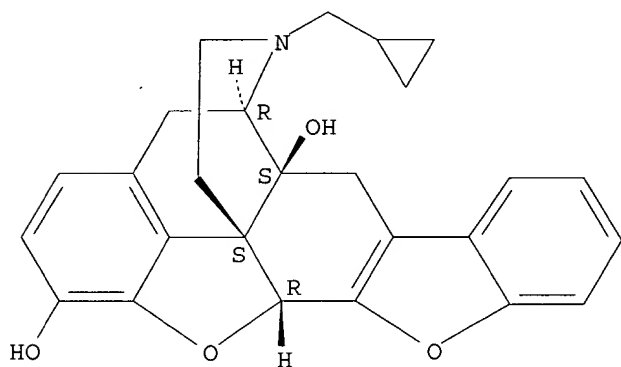
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

258 REFERENCES IN FILE CA (1962 TO DATE)
 17 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 260 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=>

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
 RN 111555-58-9 REGISTRY
 CN 4,8-Methano-8aH-bisbenzofuro[3,2-e:2',3'-g]isoquinoline-1,8a-diol,
 7-(cyclopropylmethyl)-5,6,7,8,9,14b-hexahydro-, (4bS,8R,8aS,14bR)- (9CI)
 (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN 4,8-Methano-8aH-bisbenzofuro[3,2-e:2',3'-g]isoquinoline-1,8a-diol,
 7-(cyclopropylmethyl)-5,6,7,8,9,14b-hexahydro-, [8R-
 (4bS*,8.alpha.,8a.beta.,14b.beta.)]-
 OTHER NAMES:
 CN **Naltriben**
 FS STEREOSEARCH
 MF C26 H25 N O4
 CI COM.
 SR CA
 LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT,
 CAPLUS, CHEMCATS, CSCHEM, DDFU, DRUGU, EMBASE, MEDLINE, TOXCENTER,
 USPATFULL
 (*File contains numerically searchable property data)

Absolute stereochemistry.



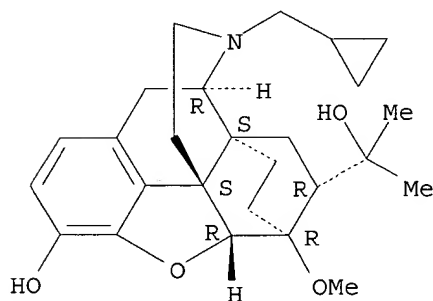
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

53 REFERENCES IN FILE CA (1962 TO DATE)
 1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 55 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=>

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
 RN 14357-78-9 REGISTRY
 CN 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-.alpha.,.alpha.-dimethyl-, (5.alpha.,7.alpha.)- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN 6,14-endo-Ethanotetrahydrooripavine, 21-cyclopropyl-7.alpha.-(1-hydroxy-1-methylethyl)- (8CI)
 OTHER NAMES:
 CN 1-N-Cyclopropylmethyl-6,7,8,14-tetrahydro-6,14-endoethano-7-(2'-hydroxy-2'-propyl)nororipavine
 CN **Diprenorphine**
 CN M 5050
 CN M 5050 Injection
 CN N-(Cyclopropylmethyl)-19-methylnororvinol
 CN RX 5050M
 FS STEREOSEARCH
 DR 11116-36-2, 17822-04-7, 37380-92-0
 MF C26 H35 N O4
 CI COM
 LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PROMT, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

396 REFERENCES IN FILE CA (1962 TO DATE)
 3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 396 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=>

L12 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS

RN 79617-96-2 REGISTRY

CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-,
(1S,4S)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-,
(1S-cis)-

OTHER NAMES:

CN (+)-Sertraline

CN CP 51974

CN **Sertraline**

FS STEREOSEARCH

MF C17 H17 Cl2 N

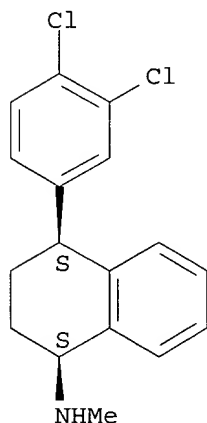
CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB,
CEN, CHEMCATS, CHEMINFORMRX, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT,
DRUGU, DRUGUPDATES, EMBASE, HSDB*, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR,
PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2,
USPATFULL

(*File contains numerically searchable property data)

Other Sources: WHO

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

816 REFERENCES IN FILE CA (1962 TO DATE)

3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

818 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=>

L17 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

AN 1998:785786 CAPLUS

DN 130:21652

TI **Substance dependence** treatment using opiate antagonists and serotonin compounds

IN Krishnan-Sarin, Suchitra; O'Malley, Stephanie; Farren, Conor

PA Yale University, USA

SO PCT Int. Appl., 20 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-44

CC 4-7 (Toxicology)

Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	---	-----	-----	-----
PI	WO 9852565	A1	19981126	WO 1998-US10289	19980519
	W: AU, CA, JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9875824	A1	19981211	AU 1998-75824	19980519
	EP 1011671	A1	20000628	EP 1998-923558	19980519
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002508753	T2	20020319	JP 1998-550563	19980519
PRAI	US 1997-46162P	P	19970520		
	WO 1998-US10289	W	19980519		
AB	Patients are treated for alc., marijuana, cocaine, opiate and polysubstance dependency by administration of combination of an effective amt. of an opioid antagonist such as nalmefene, naloxone, naltrexone, or a mixt. of any of these, and a serotonergic medication, such as sertraline, fluoxetine, paroxetine, fluvoxamine, or ondansetron. Administration of an effective amt. of an opioid antagonist alone helps to prevent relapse after detoxification is complete, and addn. of the serotonergic medication increases the effectiveness, decreases the side effects of the opioid antagonist, and also helps relieve effects of withdrawal.				
ST	alcoholism treatment opiate antagonist serotonin compd; ethanol dependence opiate antagonist serotonin compd				
IT	Drugs of abuse				
	(abuse of; substance dependence treatment using opiate antagonists and serotonin compds.)				
IT	Cannabis sativa				
	(marijuana; substance dependence treatment using opiate antagonists and serotonin compds.)				
IT	Alcoholism				
	(substance dependence treatment using opiate antagonists and serotonin compds.)				
IT	Opioids				
	RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (substance dependence treatment using opiate antagonists and serotonin compds.)				
IT	64-17-5; Ethanol, biological studies				
	RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (dependence; substance dependence treatment using opiate antagonists and serotonin compds.)				
IT	50-36-2, Cocaine				
	RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (substance dependence treatment using opiate antagonists and serotonin compds.)				
IT	458-24-2, Fenfluramine	465-65-6, Naloxone	3239-44-9	16590-41-3,	
	Naltrexone	31677-93-7, Wellbutrin	36505-84-7, Buspirone	54739-18-3,	
	Fluvoxamine	54910-89-3, Fluoxetine	55096-26-9, Nalmefene	56775-88-3,	

Zimeldine 59729-33-8, Citalopram 61869-08-7, Paroxetine 72714-74-0,
Viqualine 79617-96-2, Sertraline 83928-76-1, Gepirone
99614-02-5, Ondansetron

RL: THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(**substance dependence** treatment using opiate
antagonists and serotonin compds.)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

- (1) Kitchell; US 5486362 A 1996 CAPLUS
- (2) Norden; US 5114976 A 1992 CAPLUS

=>

L17 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS

AN 2000:861482 CAPLUS

DN 134:32977

TI Methods and compositions for the treatment of neuroleptic and related disorders using sertindole derivatives

IN Jerussi, Thomas P.

PA Sepracor Inc., USA

SO PCT Int. Appl., 33 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-00

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1, 28

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000072837	A2	20001207	WO 2000-US14984	20000531
	WO 2000072837	A3	20010517		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	US 6489341	B1	20021203	US 2000-580492	20000530
PRAI	US 1999-137447P	P	19990602		
	US 2000-580492	A	20000530		
AB	The invention relates to novel methods using, and pharmaceutical compns. and dosage forms comprising, sertindole derivs. Sertindole derivs. include, but are not limited to, nor-sertindole, 5-oxo-sertindole, dehydro-sertindole, and dehydro-nor-sertindole. The methods of the invention are directed to the treatment and prevention of neuroleptic and related disorders such as, but are not limited to, psychotic disorders, depression, anxiety, substance addiction , memory impairment and pain. For example, capsules were prep'd. contg. a sertindole deriv. 50.0 mg, lactose 48.5 mg, TiO2 0.5 mg, and Mg stearate 1.0 mg.				
ST	sertindole deriv prepn delivery system antipsychotic; anxiolytic sertindole deriv prepn delivery system; analgesic sertindole deriv prepn delivery system; antidepressant sertindole deriv delivery system; drug withdrawal sertindole deriv delivery system				
IT	5-HT receptors RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (5-HT2A, binding to; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)				
IT	Dopamine receptors RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (D2, binding to; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)				
IT	Dopamine receptors RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (D4, binding to; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)				
IT	Nervous system stimulants Psychotomimetics (addiction and withdrawal; prepn. and compns. of sertindole derivs. for				

treatment of neuroleptic and related disorders)

IT Opioids
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (addiction and withdrawal; prepn. and compns. of sertindole derivs. for
 treatment of neuroleptic and related disorders)

IT Mental disorder
 (affective; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Cholinergic agonists
 (analgesics; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Tachykinin receptors
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (antagonists; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Heart, disease
 (arrhythmia; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Drug delivery systems
 (buccal; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Development, mammalian postnatal
 (child; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Mental disorder
 (cognitive, age-related; prepn. and compns. of sertindole derivs. for
 treatment of neuroleptic and related disorders)

IT Cardiovascular system
 (disease; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Cognition
 (disorder, age-related; prepn. and compns. of sertindole derivs. for
 treatment of neuroleptic and related disorders)

IT Memory, biological
 (disorder; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Aging, animal
 (elderly; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Heart, disease
 (failure; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Mental disorder
 (hysteria, psychosis; prepn. and compns. of sertindole derivs. for
 treatment of neuroleptic and related disorders)

IT Mental disorder
 (manic bipolar disorder; prepn. and compns. of sertindole derivs. for
 treatment of neuroleptic and related disorders)

IT Drug delivery systems
 (mucosal; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Nerve, disease
 (neuropathy, pain; prepn. and compns. of sertindole derivs. for
 treatment of neuroleptic and related disorders)

IT Anti-inflammatory agents
 (nonsteroidal; prepn. and compns. of sertindole derivs. for treatment
 of neuroleptic and related disorders)

IT Drug delivery systems
 (oral; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT Drug delivery systems
 (parenterals; prepn. and compns. of sertindole derivs. for treatment of
 neuroleptic and related disorders)

IT 5-HT agonists

Adrenoceptor agonists
 Alcoholism
 Amnesia
 Analgesics
 Antiarrhythmics
 Antidepressants
 Antihypertensives
 Antipsychotics
 Antipyretics
 Anxiolytics
 Cognition enhancers
 Drug dependence
 Drug withdrawal
 Hypertension
 Obesity
 Schizophrenia
 Tobacco smoke
 (prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT Mental disorder
 (psychosis, Cheyne-Stokes; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT Arteriosclerosis
 Menopause
 Mental disorder
 (psychosis; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT Drug delivery systems
 (sublingual; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT Drug delivery systems
 (topical; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT Drug delivery systems
 (transdermal; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT Antidepressants
 (tricyclic; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT Adrenoceptors
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (.alpha.1, binding to; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT Adrenoceptor antagonists
 (.alpha.1-; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT 50-36-2, Cocaine 54-11-5, Nicotine 58-25-3, Chlordiazepoxide
 64-17-5, Ethanol, biological studies 67-52-7D, 2,4,6(1H,3H,5H)-
 Pyrimidinetrione, derivs. 72-44-6, Methaqualone 77-21-4, Glutethimide
 113-18-8, Ethchlorvynol 125-64-4, Methypylon 300-62-9D, Amphetamine,
 derivs. 439-14-5, Diazepam 604-75-1, Oxazepam 846-50-4, Temazepam
 28981-97-7, Alprazolam
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (addiction and withdrawal; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT 9002-17-9, Xanthine oxidase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (inhibitors; prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT 138900-27-3P
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
 (prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT 106516-07-8P 106516-24-9DP, Sertindole, derivs. 168274-35-9P
 173294-84-3P
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
 (prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT 106516-24-9, Sertindole
 RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT 50-47-5, Desipramine 50-48-6 50-49-7, Imipramine 50-78-2, Aspirin 53-86-1, Indomethacin 60-99-1, Methotrimeprazine 72-69-5, Nortriptyline 103-90-2, Acetaminophen 315-30-0, Allopurinol 361-37-5, Methysergide 22071-15-4, Ketoprofen 54910-89-3, Fluoxetine 61869-08-7, Paroxetine 74103-06-3, Ketorolac 79617-96-2, Sertraline 85650-52-8, Mirtazapine 93413-69-5, Venlafaxine 116539-59-4, Duloxetine
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
 (prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT 540-49-8, 1,2-Dibromoethylene 1943-83-5, 2-Chloroethylisocyanate 41979-39-9, 4-Piperidone hydrochloride 180911-99-3
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT 138900-22-8P, 1-(4-Fluorophenyl)-5-chlorindole 168274-49-5P
 170232-37-8P 311330-26-4P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (prepn. and compns. of sertindole derivs. for treatment of neuroleptic and related disorders)

IT 50-67-9, Serotonin, biological studies 51-41-2, Norepinephrine
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (reuptake inhibitors; prepn. and compns. of sertindole derivs. for treatment of neuroleptic

Enter "Y" if you wish to replace the current saved name with a new definition. Enter "N" if the current saved definition must be preserved. You may then reenter the SAVE command with a different saved name. Enter "DISPLAY SAVED" at an arrow prompt (=>) to see a list of your currently defined saved names.

REPLACE OLD DEFINITION? Y/(N):y

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FILE 'USPATFULL, CAPLUS' ENTERED AT 16:12:58 ON 25 MAR 2003

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TOTAL FOR ALL FILES
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TOTAL FOR ALL FILES
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TOTAL FOR ALL FILES
L18          8 S L15 AND SEROTONIN AND COMBIN?
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TOTAL FOR ALL FILES
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L25          5 FILE USPATFULL
L26          1 FILE CAPLUS
TOTAL FOR ALL FILES
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           SAVE ALL L0901362/L
L28        2551 FILE USPATFULL
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L30       23109 S NALOXONE OR NALTREXONE OR CYCLOZZOCINE OR DIPRENORPHINE OR ET
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TOTAL FOR ALL FILES
L36       7316 S ADDICTION
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L40 6 FILE USPATFULL
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L42 29 S L33 AND L12
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L43 51 FILE USPATFULL
L44 524 FILE CAPLUS
TOTAL FOR ALL FILES
L45 575 S L30 (1S) L9
L46 0 FILE USPATFULL
L47 0 FILE CAPLUS
TOTAL FOR ALL FILES
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L18 ANSWER 7 OF 8 USPATFULL

AB Disclosed are dopamine agonist and opioidergic compositions and methods for their use in the treatment of alcoholism. The invention discloses compounds and therapeutic kits useful in the treatment of alcoholics having the A1 allele of the dopamine receptor D2 gene. Also disclosed are methods of treating alcoholics having the A1/A1 or A1/A2 DRD2 genotype comprising administration of dopamine agonists such as aporphines, ergolines, related compounds, and their analogs, in **combination** with opioidergic compounds such as naloxone.

SUMM Intl. Pat. Appl. Publ. No. WO 9609047A1 (specifically incorporated herein by reference) discloses a method for treating alcoholism in a mammal using a **combination** of opioid antagonists and **serotonin** reuptake inhibitors.

SUMM Whereas ethanol consumption involves several brain neurotransmitters including norepinephrine (Ahlenius et al., 1973; Amit and Brown, 1982; Brown and Amit, 1977; Corcoran et al., 1983; Davis et al., 1979; Murphy et al., 1985), **serotonin** (McBride et al., 1988; Murphy et al., 1988) and GABA (Hwang et al., 1990; McBride et al., 1990), growing evidence, derived from the administration of neurotransmitter receptor agonists and antagonists, further supports an important role for the dopaminergic system in mediating the stimulating reinforcing effects of ethanol.

SUMM How naltrexone exerts its effects in humans remains yet to be determined. In a recent study, Swift et al. (1994) quantified the effects of naltrexone on alcohol intoxication in nonalcoholic humans. They found less positive reinforcement and more intense sedative effects when the subjects received naltrexone and ethanol as compared to subjects who received placebo and ethanol. The **combination** of naltrexone and ethanol also induced nausea and vomiting in some of the subjects. These findings are consistent with the idea that naltrexone alters the subjective effects of ethanol. In particular, naltrexone reduces the positive reinforcing effects of ethanol intoxication and increases the negative reinforcing effects. Swift et al. (1994) suggest that these changes may underlie the observed decrease in ethanol drinking reported in the above clinical trials.

SUMM In 1990, the present inventor and colleagues reported (Blum et al., 1990) a molecular genetic association with alcoholism. Specifically, the A1 (minor) allele of the D.sub.2 dopamine receptor (DRD2) gene was found to be associated with severe alcoholics when compared to nonalcoholic controls. Subsequently, several studies, done in the U.S. and abroad, have further ascertained the role of this gene in alcoholism. Despite variations in the selection of subjects and other methodological issues, the **combined** evidence from these studies affirms the high prevalence of the A1 allele in alcoholics, especially when severe alcoholics are compared to nonalcoholic controls. Similarly, studies on cocaine addicts and polysubstance abusers have also found a high prevalence of the minor (A1 and B1) alleles of the DRD2 gene in these patients (Noble et al., 1993; Comings et al., 1991; Smith et al., 1992). Binding studies on the brains of deceased subjects showed that those carrying the A1 (minor) allele had reduced number of D.sub.2 receptors than those carrying the A2 (major) allele (Noble et al., 1991). Moreover, in recent neurophysiological Noble et al., 1994c) and neuropsychological (Berman and Noble, 1995) studies of alcohol- and other drug-naive children, evidence also suggests a reduced dopaminergic function in subjects carrying the A1 allele compared to those having only the A2 allele. Put together, the emerging data suggest that subjects who inherit the A1 allele have an inherent deficit of their brain dopaminergic system.

SUMM In a second embodiment, the treatment may further involve the

administration of a **serotonin** reuptake inhibitor. Such an inhibitor may be fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, and nefazodone; or a salt or an analog or a derivative thereof.

SUMM A further aspect of the invention is a method of treating alcohol addiction. This method generally involves identifying an alcoholic subject having a DRD2 A1 allele; and administering to the subject an amount of a DRD2-specific dopamine agonist composition sufficient to alleviate said alcohol addiction. Preferably the A1 allele has an A1/A1 or A1/A2 genotype. Preferred dopamine agonists include ergolines or aporphines. Optionally, the method may further comprise the administration of a second agonist compound, or alternatively, the administration of one or more of the opioidergic compositions disclosed herein, either alone, or in **combination** with one or more of the **serotonin** reuptake inhibitors described herein. Preferably, the opioidergic compositions are naloxone, naltrexone, naloxone methiodide, naloxonazine, naltrindole, naltrindole isothiocyanate, naltriben, norbinaltorphimine, funaltrexamine, cyprodime, cyclozzocine, diprenorphine, etazocine, levalorphan, metazocine, spiroindane, nalmefene, or nalorphine, or salts, analogs, or derivatives thereof. The serotonin reuptake inhibitors are preferably selected from the group consisting of fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, and nefazodone.

SUMM The method may further comprise administering to the human one or more opioidergic compositions either alone or in **combination** with one or more **serotonin** reuptake inhibitors.

SUMM There are certain considerations that appear to be important in designing compositions which interact with the DRD2 receptor, and which particularly result in amelioration of alcoholic behavior in patients having the DRD2 A1 (or minor) allele. In addition to ergot-related structures such as the ergolines and their derivatives, aporphines and aporphine analogs are also expected to provide a suitable nucleus for modification. These compounds mimic dopamine to the extent of exhibiting ortho hydroxyl groups on an aromatic ring and it might be expected that bromo substituents will confer allelic specificity in a manner similar to that observed with bromocriptine. Other functional groups appear also to affect binding characteristics, particularly substituted ureas, secondary amides and thio ethers. In **combination** with rigid structures, these groups may be encouraged to bind with the DRD2 receptor. Rigid nuclei need not be aromatic; for example, bridged species such as adamantane or tricyclic compounds may provide any requisite rigidity.

SUMM 2.4 SELECTION OF **SEROTONIN** REUPTAKE INHIBITORS

SUMM The selection of **serotonin** reuptake inhibitors for use in the methods and compositions of the present invention are also well-known to those of skill in the art. For example, the teachings of Intl. Pat. Appl. Publ. No. WO 9609047A1, specifically incorporated herein by reference) provides one of skill in the art, having benefit of the present specification, to select **serotonin** reuptake inhibitory compounds which would be useful in the methods and compositions described herein. Preferred **serotonin** reuptake inhibitory compounds for use in the present invention include, but are not limited to, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, and nefazodone, and salts or analogs thereof.

SUMM In an important aspect, the invention provides a therapeutic kit comprising, in suitable container means, a therapeutically-effective amount of a DRD2-specific dopamine agonist, and a pharmaceutically acceptable excipient. Alternatively, the kit may further provide one or

more opioidergics and/or one or more **serotonin** reuptake inhibitors in a single or distinct container means. The compositions may be formulated such that they are suitable for oral or parenteral administration.

- SUMM Additionally, the composition may further comprise a **serotonin** reuptake inhibitor selected from the group consisting of fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, and nefazodone, or salts, analogs, or derivatives thereof
- SUMM A further aspect of the invention is a composition which comprises at least two dopamine agonists (which are specific for the DRD2 dopamine receptor) and one or more opioidergics in a pharmaceutically-acceptable excipient. In a preferred embodiment, at least one of the dopamine agonists is bromocriptine. The opioidergics may be selected from the group consisting of naloxone, naltrexone, naloxone methiodide, naloxonazine, naltrindole, naltrindole isothiocyanate, naltriben, norbinaltorphimine, funaltrexamine, cyprodime, cyclozocine, diprenorphine, etazocine, levalorphan, metazocine, spiroindane, nalmefene, and nalorphine, or salts, analogs, or derivatives, thereof. The composition may further include one or more **serotonin** reuptake inhibitors, such as fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, nefazodone, or salts, analogs, or derivatives thereof
- SUMM In another aspect of the invention, there is provided a composition comprising at least two dopamine agonists, wherein both dopamine agonists are specific for the DRD2 dopamine receptor, one or more opioidergics, and a **serotonin** reuptake inhibitor in a pharmaceutically-acceptable excipient. In a preferred embodiment, at least one of the dopamine agonists is bromocriptine. The opioidergics may be selected from the group consisting of naloxone, naltrexone, naloxone methiodide, naloxonazine, naltrindole, naltrindole isothiocyanate, naltriben, norbinaltorphimine, funaltrexamine, cyprodime, cyclozocine, diprenorphine, etazocine, levalorphan, metazocine, spiroindane, nalmefene, and nalorphine, or salts, analogs, or derivatives, thereof. The composition may further include one or more **serotonin** reuptake inhibitors, such as fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, nefazodone, or salts, analogs, or derivatives thereof
- DRWD The drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in **combination** with the detailed description of specific embodiments presented herein.
- DETD The present invention represents a significant benefit to the field of alcoholism and an improvement of the state of the art in the field. By providing unique compositions and methods, the invention provides an effective and targeted pharmacological treatment for a certain severe molecular genetic type (DRD2 A1 allele) of alcoholics. Such an approach may also provide compositions and methods for the treatment of other **drug dependencies** which involve the dopaminergic system.
- DETD The methods of the present invention generally involve obtaining a blood sample from a patient suspected of being an alcoholic, then genotyping the D2 receptor alleles. For those alcoholics with the genetic form of the disease (i.e. those who carry the A1 allele), a treatment regimen is then coupled to this diagnosis which provides the greatest improvement in alcoholism of such an A1-allele carrying subject. In one such treatment method, the treatment consists of administration of therapeutically-effective amounts of either a dopaminergic composition such as bromocriptine (e.g., in an amount of 2.5 mg given three times daily), or an opioidergic composition such as naloxone or naltrexone

(e.g., in an amount of 50 mg daily). In one embodiment, the treatment method comprises administration of a single dopaminergic composition alone. Alternatively, a **combination** of one or more dopaminergic compounds may be administered either alone or in **combination** with one or more opioidergic compounds. In a further alternative, a single opioidergic compound (e.g., naloxone or naltrexone) may be administered to A1 allele patients.

DETD Recent studies (Neiswanger et al., Am. J. Med. Genet. 60:267-271; 60:272-275, 1995) have confirmed the association of the DRD2 TaqI A1 allele and compulsive disorders such as alcoholism. Linkage and association studies were performed using alcoholic men from high-density families largely uncontaminated by other psychopathology, and female alcoholics who also suffered from secondary **drug dependence**. Neiswanger et al, concluded "the original positive association of the TaqI A1 allele to alcoholism (Blum et al., 1990) has been replicated several times (Blum et al., 1991; Parsian et al., 1991; Comings et al., 1992; Amadeo et al., 1993; Neiswanger et al., 1995). With careful construction of control groups, e.g., the use of both carefully diagnosed random controls and `super-normal` controls, population-based association studies also have the potential to help detect genetic risk factors which might go unidentified using other means. Hence it is advantageous to use the lessons of the DRD2 controversy to adapt this experimental approach to the specific challenges presented by psychiatric genetics, rather than dismiss it prematurely."

DETD The changes in craving scores in this sample of alcoholics are presented in FIG. 1. The changes in the two treatment (BRO, PLA) and the two allele (A1, A2) groups are shown in FIG. 1A. The changes in the four treatment/allele groups (BRO A1, BRO A2, PLA A1, PLA A2) are shown in FIG. 1B. No significant treatment or allele effect on craving or treatment.times.allele interaction for craving was found in the interval of 0-3 weeks. However, in the interval of 3-6 weeks a significant treatment effect was obtained ($P=0.027$), with craving scores decreasing by 34.0% in the BRO group compared with 8.5% in the PLA group (FIG. 1A). Furthermore, during the interval of 3-6 weeks, there was a significant treatment.times.allele interaction ($P=0.011$). Specifically, the decrease in craving scores was greatest in the BRO A1 (68.0%) group compared with the BRO A2 (10.2%), the PLA A1 (-14.3%) and the PLA A2 (13.9%) groups (FIG. 1B). Preplanned comparison showed this decrease to be more than sixfold greater in the BRO A1 compared with the other three treatmentlallele groups **combined** ($P=0.003$).

DETD The changes in anxiety scores for the two treatment, two allele and four treatment/allele groups are shown in FIG. 2. In the interval of 0-3 weeks, there was no significant treatment or allele effect or treatment.times.allele interaction. However, in the four treatment/allele groups, the decrease in anxiety scores was greatest in the BRO A1 (14.8%) group compared with the BRO A2 (-0.4%), the PLA A1 (-0.8%) and the PLA A2 (-6.6%) groups (FIG. 2B). Preplanned comparison showed the decrease in anxiety, like the craving scores, was significantly greater in the BRO A1 group compared with the BRO A2 group ($P=0.013$). Furthermore, the decrease in anxiety scores was also significantly greater in the BRO A1 group compared with the other three treatment/allele groups **combined** ($P=0.004$). However, in the interval of 3-6 weeks, changes in anxiety scores were not significantly differentiated among the four treatment allele groups.

DETD There was also no significant difference in this measure among the four treatnmentlallele groups. When the interval of 3-6 weeks was examined, the attrition to retention ratio of the patients was lower for the BRO group (8/35) than the PLA group (11/17). However, the difference between these two groups was not significant (.chi..sup.2 =2.72, $P=0.099$). When the four treatment/allele groups were examined, the attrition to retention ratio increased progressively in the BRO A1 (3/14), BRO A2 (5/21), PLA A2 (4/13) and PLA A1 (7/4) groups in that order. Moreover, there was a significant difference among these four groups (.chi..sup.2

=9.20, P=0.027). Post hoc analysis showed the attrition to retention ratio was significantly higher in the PLA A1 than in the BRO A1 group (.chi..sup.2 =4.31, P=0.038). Finally, this ratio in the PLA A1 group was also significantly higher than in the other three treatment allele groups **combined** (.chi..sup.2 =6.94, P=0.008).

DETD Craving, an obsessive desire for alcohol, is a common experience in alcoholics and has been viewed as an important determinant of relapse. In this study, the effect of BRO in reducing craving was manifested after about three weeks of treatment, a finding also observed by Borg (1983). This reduction was significantly greater in the BRO A1 group than its key comparative BRO A2 group, and also significantly greater when compared with the other three treatment/allele groups **combined**. Likewise, the reduction in anxiety in the BRO A1 group was significantly greater when compared either with the BRO A2 group or with the other three treatment/allele groups **combined**. However, the effect on anxiety in the BRO A1 group occurred before (0-3 weeks) the effect on craving (3-6 weeks). Whether there is a causal connection between the reduction in anxiety and the reduction in craving in the BRO A1 group remains to be determined.

DETD Charness et al. "Ethanol increases the expression of functional **delta-opioid** receptors in neuroblastoma.times.glioma NG 108-15 hybrid cells," J. Biol. Chem., 261:3164-3169, 1986.

DETD Gongwer et al., "Regional Brain Contents of **Serotonin**, Dopamine and Their Metabolites in the Selectively Bred High- and Low-Alcohol Drinking Lines of Rats," Alcohol, 6:317-320, 1989.

DETD Hynes et al. "Chronic ethanol alters the receptor binding characteristics of the **delta opioid** receptor ligand, D-Ala.sup.2,D-Leu.sup.5 enkephalin in mouse brain," Life Sci., 33:2331-2337, 1983.

DETD Koob and Bloom. "Cellular and molecular mechanisms of **drug dependence**," Science 242:715-723, 1988.

DETD McBride et al., "**Serotonin**, Dopamine and GABA Involvement in Alcohol Drinking of Selectively Bred Rats," Alcohol, 7:199-205, 1990.

DETD Noble et al., "Allelic Association of the D.sub.2 Dopamine Receptor Gene with cocaine **Dependence**," Drug Alc. Depend., 33:271-285, 1993.

DETD Yoshimoto et al., "Alcohol Stimulates the Release of Dopamine and **Serotonin** in the Nucleus Accumbens," Alcohol, 9:17-22, 1991.

CLM What is claimed is:

4. The method of claim 1, further comprising administering to said human a **serotonin** reuptake inhibitor selected from the group consisting of fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, and nefazodone.

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